Public Health
Seattle & King County

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Targeted testing and treatment for latent TB infection

Introduction

The Centers for Disease Control and Prevention and the American Thoracic Society published new guidelines for targeted testing and treatment for latent TB infection (LTBI) in the spring of 2000. The Advisory Council for the Elimination of TB and the Institute of Medicine of the National Academy of Sciences also published reports in 1999 and 2000 that advise major expansion of targeted testing and treatment efforts as one of the crucial means of progressing toward TB elimination. This statement summarizes the current approach of the TB control program of Public Health, Seattle and King County to these guidelines and directives. This approach is based on an interpretation of the available scientific literature, local epidemiology, previous screening guidelines, program experience, and an acknowledgement of limited resources. It also encourages a current trend to increase targeted testing and treatment for latent TB infection in primary care settings.

Definitions

- **Targeted testing**
  "Targeted tuberculin testing for LTBI is a strategic component of tuberculosis (TB) control that identifies persons at high risk for developing TB who would benefit by treatment of LTBI, if detected. Persons with increased risk for developing TB include those who have had recent infection with Mycobacterium tuberculosis and those who have clinical conditions that are associated with an increased risk for progression of LTBI to active TB." (ATS/CDC 2000) In some settings in King County, persons are also tested as an initial screening measure to trigger further evaluation for TB disease, to comply with state and federal requirements for employment or for change of immigration status.

- **ATS Classification of TB diagnoses**
  0: no TB exposure, not infected
  1: TB exposure, no evidence of infection
  2: latent TB infection, no disease (LTBI)
  3: tuberculosis, clinically active
  4: tuberculosis, not clinically active
  5: tuberculosis suspect (diagnosis pending)
  MOTT: Mycobacteria other than TB

- **Latent TB infection**
  Persons with LTBI have evidence of TB infection based on a tuberculin skin test reaction that has been professionally interpreted to be positive and have no clinical, bacteriological or radiographic evidence of active TB. Persons with HIV infection or other severe immunosuppression may be diagnosed to have LTBI even though a tuberculin skin test is negative if they are contacts of an infectious case of TB and have no evidence of active TB. Persons with LTBI have a 5% to 10% lifetime risk of developing active TB, half of which is in

the first year after becoming infected. Persons with HIV infection and LTBI have up to a 7% per year chance of developing active TB. Neither the state of Washington nor Seattle and King County require reporting of persons with LTBI, although reporting of TB infection is required in Pierce County. LTBI is a chronic medical condition that belongs on a patient's primary care problem list, even if it has been treated.

- **Treatment for latent TB infection**
  Treatment regimens have been shown to have 60% to 90% effectiveness at reducing the chance of developing active TB. Roughly speaking, if a person with LTBI has a 10 % lifetime risk of developing TB without treatment, after completion of treatment for latent TB infection this risk drops to approximately 1%. Although it may be strongly advised, treatment of LTBI is not legally required in Washington State.

Tuberculin skin test interpretation
Tuberculin skin tests, Mantoux method only, are interpreted based on the professionally measured size of induration at 48 to 72 hours. The size of induration considered to indicate TB infection depends on the nature and extent of the risk of future disease, those at highest risk being read as positive at the lowest cutting point. Sometimes the cut-off size for which a chest x-ray is legally required is different from the size that is determined clinically to indicate infection.

Skin test read as positive at 5mm:
1. contact of an infectious case
2. known or suspected HIV infection
3. abnormal chest x-ray with fibrotic lesions suggestive of inactive pulmonary tuberculosis (not including isolated calcifications or minimal pleural thickening)
4. organ transplantation and other heavily immunosuppressed patients

Note: Civil surgeons and the county jail are required by their own guidelines to get chest x-ray evaluation on all persons they serve who are found to have reactions of 5 mm or more, even though they may be determined not to have TB infection.

Skin test read as positive at 10mm:

1. persons with immunosuppressive medical conditions other than HIV infection, including diabetes, renal insufficiency, gastrectomy, corticosteroid therapy (> 15 mg/day of prednisone for 2 weeks), and other immunosuppressive therapy and conditions
2. Persons who develop a new positive skin test and an increase of 10 mm or more in size of the skin test reaction within a 2 year period ("recent converter").
3. Persons who within the past 5 years have lived in or traveled extensively in areas of the world where TB is endemic including most of Asia, Africa and Latin America. Asian countries of the former Soviet Union, Albania, Bulgaria, Moldova and Romania are considered to be endemic areas with a 10 mm cutoff for diagnosing TB infection. (Countries of former Yugoslavia are not considered by the King County Public Health TB Program to be in this category, although they were during and shortly after the wars in that region.)
4. homeless persons, if recent transmission of TB has been demonstrated in their setting
5. persons who live in some congregate settings, or have done so in the last 2 years, voluntarily, such as in assisted living or drug treatment programs, or involuntarily, such as in jails, prisons or refugee camps
6. persons in substance abuse treatment programs, if recent transmission of TB has been demonstrated.
7. persons in certain occupations, including health care workers and others who work with large numbers of persons at risk of tuberculosis

Note: Persons starting certain jobs, such as day care and nursing home work are required to get chest x-ray evaluation if they are found to have reactions of 10 mm or more, even though they may be determined not to have TB infection.

Skin test read as positive at 15mm:

1. Persons who are not in the above high-risk categories. In general persons without high risk are advised not to undergo tuberculin skin testing because of the high false-positivity rate in groups with low prevalence of TB infection. Persons from countries with established market economies and persons from countries of the former European socialist economies are considered to have TB infection if their skin test reactions are larger than 15 mm.

Other persons who receive screening services at the TB clinic and are found to have LTBI but are not in these highest priority groups are advised to discuss treatment for LTBI with their private medical provider or to seek further care at one of a list of medical clinics that have agreed to treat persons for latent TB infection regardless of their ability to pay.

Indications for testing

Persons in the high-risk groups listed above should receive tuberculin skin testing. Those who are found to have negative skin tests but who remain in high-risk settings, such as health care workers, should have periodic follow-up skin testing, in order to achieve early detection of new TB infection.

Contacts

Contacts of persons with infectious TB are the most important persons to test for TB infection. A contact who is determined to be at risk for new infection is generally determined to have TB infection if the skin test shows > 5 mm induration. Degree of risk is usually determined in the context of the details and findings of the TB control program's contact investigation. Household contacts of infectious cases are usually offered a CXR in addition to the skin test. Treatment is usually recommended for contacts with TB infection in whom TB disease has been ruled out. Treatment is also recommended for the highest risk persons - HIV infected and those younger than 5 years old - even though a skin test is negative, once TB disease has been ruled out. Persons with an initial negative skin test are also offered a repeat skin test about 3 months after the contact has been "broken," which may mean the day the source case starts treatment. 3 months is after the end of the 10-day to 10-week incubation period for developing a positive skin test. Small children who have negative skin tests at 3 months can be taken off TLTBI at that time. HIV-infected contacts are usually advised to complete a course of TLTBI regardless of the 3-month skin test result.

BCG

Targeted testing and treatment for LTBI should be performed regardless of a patient's history of BCG vaccination. Please also see our webpage on BCG Vaccination.

Two-step testing

Persons who are starting work in settings where follow-up skin test screening on a periodic basis will be performed, are not known to have a prior-positive skin test, have not had a tuberculin skin test within the previous one year (by OSHA and WISHA requirements) and have an initial negative skin test, should have a second skin test placed one to three weeks later. If this second step test shows a positive response, it may demonstrate a boosted response to an old infection. Since boosting can last up to a year or two, the two-step test reduces the likelihood that repeated

skin testing might falsely indicate new infection in an ongoing surveillance program of persons who are at risk for acquiring new infection. Two step testing is not recommended by the TB clinic in contact investigations.

Evaluation for TB disease

All persons found to have positive skin tests should have evaluation for TB disease. This evaluation should include a chest x-ray and an evaluation for signs and symptoms of TB disease. Persons who are found to have an abnormal chest x-ray with fibrotic lesions suggestive of inactive pulmonary tuberculosis (not including isolated calcifications or minimal pleural thickening) should have two or three spontaneous sputum samples collected to look for active pulmonary tuberculosis. No single or double-drug regimens for treatment of LTBI should be started while any cultures are pending, nor for any person who is not in a baseline state of health.

Prioritizing Treatment

Limited resources may determine the degree to which any clinician or program can institute and ensure completion of treatment of LTBI. The effort and resources that a program devotes to targeted testing and treatment of LTBI may also be determined by the degree to which each program includes protecting its community from disease as part of its mission. Each program must also choose the degree to which it can contribute to the protection of its patients and its community from future disease by minimizing barriers to a patient's starting and completing treatment. Such barriers may include requests for payment for TB-related evaluations and treatment.

a. **Highest risk groups**
   Significant efforts should be extended to ensure that persons with the highest risk, those in the 5 mm cutoff groups listed above, receive and complete treatment for LTBI.
b. **Hierarchy of lower risks**
   The TB control program in King County does not have the resources to treat all high-risk persons with latent TB infection in this community. Since the mid-1990's an effort has been made to encourage targeted testing and treatment for LTBI throughout the medical community.

The TB Clinic currently offers treatment to the following persons who are found in its program to have LTBI:

1. All persons in the 5 mm risk groups listed above
2. Persons in the 10 mm risk groups with underlying medical conditions that predispose to progression of TB
3. Children (defined as younger than 18 years old)
4. Homeless persons, because recent transmission is documented in that group (treatment partly funded by Health Care for the Homeless project)
5. Patients referred by Jail Health Services

Other persons who receive screening services at the TB clinic and are found to have LTBI but are not in these highest priority groups are advised to discuss treatment for LTBI with their private medical provider or to seek further care at one of a list of medical clinics that have agreed to treat persons for latent TB infection regardless of their ability to pay.

Treatment Regimens

a. **9 months isoniazid**
This is the preferred regimen in terms of proven efficacy and it is currently the main regimen offered by the TB clinic. In some cases it is given by twice weekly directly observed therapy. The American Academy of Pediatrics continues to recommend a 9 month course of therapy for children, as they did even when the ATS and CDC recommended 6 months of therapy as a standard regimen.

b. **2 months rifampin and pyrazinamide**
Recent reports of severe liver injury in patients taking this regimen require providers to be especially cautious and vigilant in its use. It should be avoided in persons with pre-existing liver injury or for those who have had an INH-associated liver injury. No more than a 2-week supply should be given at a time to patients, with in-person clinical assessments and blood draws for AST at 0, 2, 4, and 6 weeks of treatment.

This regimen has been shown to be as effective as a course of isoniazid in HIV-infected persons. Many experts believe it is likely to be as effective in persons not infected with HIV, including those with inactive pulmonary tuberculosis. The TB clinic is using this regimen selectively, for persons for whom a shorter regimen is thought to have advantages that outweigh the possible disadvantages of taking two medications. Sometimes it is given by twice weekly directly observed therapy.

c. **4 months rifampin**
This regimen is currently recommended by ATS/CDC as the first alternative to 9 months of INH, such as for treatment of contacts of INH-resistant TB. As with any single or even double-drug regimen for TLTBI, active disease must be ruled out to a high degree of certainty before starting treatment, in order to prevent the emergence of drug-resistant strains.

d. **6 months isoniazid**
While a 9 month course of treatment gives a greater degree of protection, a 6 month course is recognized to give significant protection against TB activation. The TB clinic no longer recommends 6 months of treatment to patients it treats, partly in the belief, not yet proven, that if a person is likely to complete 6 months of therapy he may be nearly as likely to complete 9 months of therapy and based on the belief of clinic nurses that the most effective regimen available should be the first choice recommended to patients. Some programs may determine that a 9 month regimen is too expensive or that their population or individual patients are unlikely to complete it and may choose to continue to advise 6 months of isoniazid.

e. **B6**
Pyridoxine is offered to patients on isoniazid at the TB clinic, who display significant evidence of malnutrition, those who have pre-existing symptoms of peripheral neuropathy, those who have pre-existing conditions that carry a high risk of causing peripheral neuropathy such as diabetes and HIV infection, and those who develop symptoms compatible with peripheral neuropathy while taking isoniazid.

Pregnancy

Persons found to have TB infection during pregnancy should have further evaluation for TB disease, including chest x-ray, symptom check, and a verbal or written screen for medical conditions that increase the likelihood of developing TB disease - regardless of stage of pregnancy. Contacts, recent PPD converters, and those with medical conditions that increase the likelihood of developing TB disease are advised to start a course of treatment for LTBI regardless

of pregnancy. Other pregnant women are generally advised to defer treatment of LTBI until after delivery. Breast-feeding is not a contraindication to treatment of LTBI. Symptom screening should then be repeated - and a chest x-ray if the previous film is older than 6 months - to rule out active disease before starting treatment.

The TB clinic monitors for drug toxicity in women who are pregnant or lactating just as it does for all patients. Some experts, however, advise drawing baseline and monthly LFT's in all pregnant and post-partum (up to 3 months) women on isoniazid, based on two reports of a greater risk of isoniazid-induced hepatitis in pregnant and post-partum women.

Monitoring for Toxicity

a. **Isoniazid containing regimens**
   AST (SGOT) is measured before starting isoniazid at the TB clinic in patients who have signs, symptoms or history of hepatitis. All patients are carefully instructed about signs and symptoms of hepatitis before starting isoniazid. Repeat screening for signs and symptoms and repeat instruction are given before each monthly refill of medication. Patients are instructed to stop taking isoniazid at the first sign of hepatitis symptoms and to call the clinic to arrange to have LFT's drawn as soon as possible. Isoniazid is stopped if transaminase values are three to five times above the upper limit of normal. Hepatitis virus screens and evaluation for other causes of hepatotoxicity are also performed when significant transaminase elevations are discovered.

b. **Rifampin containing regimens**
   Patients starting and continuing rifampin are screened verbally and instructed to watch for signs of bleeding disorders and for significant drug interactions. Rifampin significantly increases hepatic metabolism of methadone, coumadin, beta-blockers, oral hypoglycemics, hormonal contraceptives, protease inhibitors, and other medications. Rifampin is also a potential hepatotoxin, and screening and teaching for this complication are done as for isoniazid. A CBC with platelets is drawn if a patient shows or describes signs of unusual bruising or bleeding. Some patients on rifampin also develop a periodic flu-like syndrome, which may be more common with intermittent dosing.

c. **Pyrazinamide**
   Pyrazinamide usually causes elevated uric acid levels and sometimes causes gout. Pyrazinamide is also a potential hepatotoxin, and screening and teaching for this complication are done as for isoniazid. Uric acid levels are drawn if patients develop joint pain.

d. **Multidrug-regimens**
   The risk of drug-induced hepatitis appears to be greater in patients who are on two or more potential hepatotoxic agents. LFT's are drawn as a baseline for all patients who are starting multi-drug regimens including RIF/PZA for LTBI. Persons with abnormal baseline values that are considered to still demonstrate an adequate margin of safety to start therapy, have LFT's repeated at individually determined intervals. Verbal screening and teaching for hepatitis are repeated at each monthly visit for a refill.

Completion of Therapy

According to the current ATS/CDC guidelines: "Completion of therapy is based on total number of doses administered - not on duration of therapy alone. The 9-mo regimen of daily isoniazid should consist of 270 doses, at minimum, administered within 12 mo, allowing for minor interruptions in therapy. The 6-mo regimen of isoniazid should consist of at least 180 doses administered within 9 mo. Twice-weekly isoniazid regimens should consist of at least 76 doses

administered within 12 mo for the 9-mo regimen and 52 doses within 9 mo for the 6-mo regimen. The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses to be administered within 3 mo. The regimen of daily rifampin alone should consist of at least 120 doses administered within 6 mo."

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